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Objectives and methods of the ORCHESTRA FOUNDATION Registry study: a multicenter observational study of the use of insulin pump therapy in pregnant women with type 1 diabetes mellitus in Poland

ABSTRACT

Background. The ORCHESTRA FOUNDATION Registry study was a prospective, multicenter, observational, post-market study investigating the use of an insulin pump with or without continuous glucose monitoring (CGM) [i.e., sensor-augmented pump (SAP) or sensor-integrated insulin pump (SIP)]; before, during, and after pregnancy, in women with type 1 diabetes mellitus (T1DM).

Methods. Study participants enrolled in 24 centers, in Poland, and contributed intake and follow-up data for up to 22 months (i.e., up to 12 months pre-conception, throughout pregnancy, and 6 weeks after delivery). Participants who were already pregnant were enrolled up to the 16th week of pregnancy. Investigated outcomes included HbA_{1c} before and during pregnancy, and serious adverse events (e.g., severe hypoglycemia, diabetic ketoacidosis, miscarriage, and hospitalization due to

any bleeding or any symptoms suggesting premature delivery). Routine clinical data including maternal weight, body mass index, and daily insulin use were also recorded. The insulin delivery devices used in the study were the MiniMed™ Paradigm™ REAL-Time insulin pump with CGM (via the MiniMed Sof-sensor™ sensor) or without CGM, and the MiniMed Paradigm Veo™ with CGM (via the Enlite™ sensor).

Results. Study enrollment began in May 2013 and the last patient completed the study in August 2017.

Conclusions. The ORCHESTRA FOUNDATION Registry study provides an opportunity to assess the effects of automated insulin delivery in pregnant women with T1DM using insulin pumps with or without continuous glucose monitoring. (Clin Diabetol 2018; 7, 3: 136–144)

Key words: type 1 diabetes, continuous subcutaneous insulin infusion, pregnancy, registry study, sensor-augmented pump therapy; sensor-integrated pump therapy

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Introduction

Diabetes is the most common metabolic disease complicating pregnancy, and the number of pregnancies complicated by diabetes is rising as the number of people with diabetes increases. Diabetes during

pregnancy is associated with considerable risks for both the mother and the fetus. Risks for the mother include miscarriage, hypoglycemia, ketoacidosis, preeclampsia, polyhydramnios, and premature or obstructed labor, which may necessitate caesarean section. Fetuses and neonates are at increased risk of congenital malformations, perinatal mortality, birth injuries, macrosomia, neonatal hypoglycemia, jaundice, and respiratory distress [1–8].

The relationship between glucose control before conception and the incidence of miscarriage and congenital malformations is well established [6, 9, 10]. High HbA_{1c} levels in early pregnancy are associated with complications such as congenital malformations and miscarriage, while hyperglycemia in late pregnancy is associated with macrosomia leading to birth injury and caesarean section, other fetal morbidity [1, 1–5, 8–11], and a potential predisposition to type 2 diabetes and obesity [12, 13].

Tight glucose control (HbA_{1c} < 6.0%) during pregnancy is recommended by many guidelines [7, 14, 15], but achieving such control is challenging. It is crucial to achieve near-normal glycemic control before and during pregnancy, and to mimic the patterns of glucose levels seen in normal pregnancies. However, women with type 1 diabetes mellitus (T1DM) treated with multiple daily injections (MDI) throughout pregnancy experience prolonged daily exposure to higher than recommended glucose levels, resulting in a 3–5-fold greater incidence of complications than that observed in the general population [11]. Some studies have shown that improvements in HbA_{1c} levels achieved with MDI are associated with an increased risk of severe hypoglycemia, particularly nocturnal and undetected postprandial hyperglycemia [16–18]. Severe hypoglycemia affects 25–40% of pregnant women and is 3–5 times more common in early pregnancy than in the period before pregnancy [18, 19]. In one study, intensively treated pregnant women were 15 times more likely to experience severe hypoglycemia than women receiving conventional treatment [18]. During the first trimester of pregnancy, nocturnal hypoglycemia may be present in as many as 37% of pregnant women [20]. Although hypoglycemia is more harmful to the mother than to the fetus, hyperglycemia after episodes of hypoglycemia and variable levels of glycemia may also be dangerous for the fetus [20–22].

In non-pregnant women with T1DM, continuous subcutaneous insulin infusion (CSII) has been shown to be associated with a reduced rate of severe hypoglycemia, compared with MDI therapy, without adversely affecting glycemic control [22]. Similarly, insulin pump use in pregnancy has been found to reduce HbA_{1c} levels

in patients with T1DM without increasing the rate of severe hypoglycemia or ketoacidosis [23]. Both CSII and continuous glucose monitoring (CGM), alone or in combination as a sensor-augmented pump (SAP) or sensor-integrated pump (SIP) therapy, improve glycemic control by reducing HbA_{1c} from 0.4–1.2% [24–30]. The recent INTERPRET study, the largest and longest multicenter prospective study to date, has confirmed the effectiveness of CGM in pump users; data from 263 patients using SAP therapy under real-life conditions over 12 months revealed significantly lower rates of hospitalization, greater treatment satisfaction, and reduced fear of hypoglycemia compared to CGM non-users [31]. Other studies have also shown that the use of CGM and related features such as alarms and automatic insulin suspension (i.e., low glucose suspension [LGS]) reduces fear of hypoglycemia, the incidence of severe hypoglycemic events, and time spent in hypoglycemia [32–35]. More importantly, the use of the LGS feature does not result in rebound hyperglycemia [33].

While the frequency, magnitude, and duration of hyperglycemia or its link with prior hypoglycemia, are best captured by CGM, self-management of glycemia is essential for good glycemic control in diabetic patients. Postprandial glucose levels during pregnancy show a strong association with the incidence of macrosomia [36]; and postprandial glucose monitoring and maintained glycemic targets have been shown to improve neonatal outcomes better than preprandial glucose monitoring [7]. Neonatal outcomes are more closely associated with hyperglycemic excursions, versus average daily glycemic control [37, 38]. Hence, the ability to analyze hypoglycemia and hyperglycemia with CGM may be useful in detecting anticipated neonatal outcomes.

In summary, pump therapy, particularly that involving use of SAP or SIP systems, provides the technology to facilitate reduction of HbA_{1c} before and during pregnancy. Such therapy can alert the mother to glucose excursions, and assist in preventing severe hypoglycemic events without incurring the risk of rebound hyperglycemia. For this reason, the Orchestra Foundation (Wielka Orkiestra Świątecznej Pomocy) funded the ORCHESTRA Registry study, to determine effectiveness of CSII therapy with and without CGM in pregnant women, in Poland. The design and methodology of this study are described in this paper.

Research design and methods

The study protocol was approved by Central Ethics Committee, and was valid for all participating centers. No Competent Authority approval was required for observational studies in Poland.

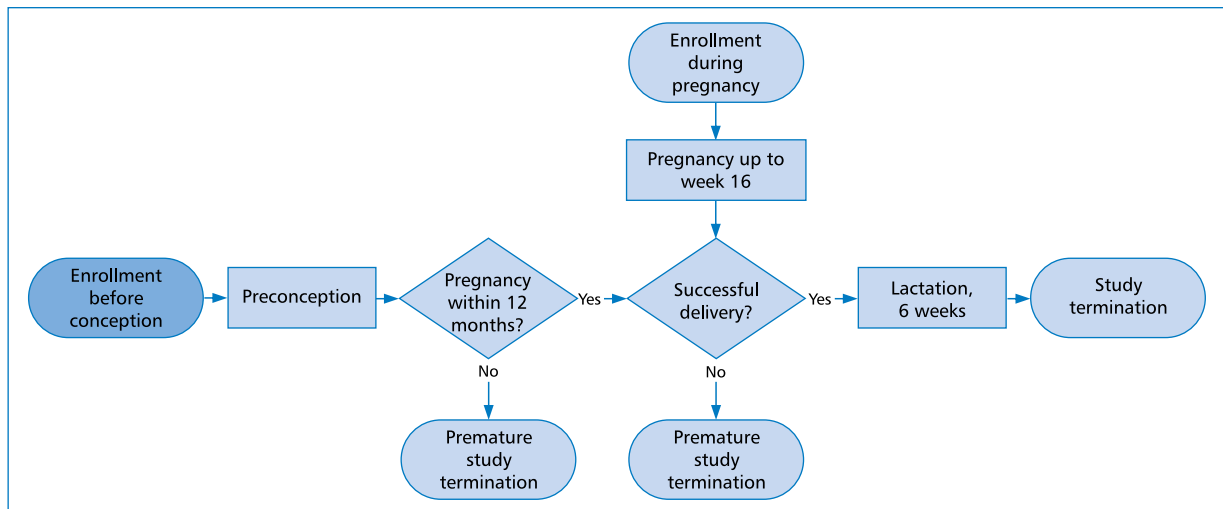


Figure 1. Study enrollment and termination procedures

Investigators and study duration

In total, 24 centers in Poland, identified by the Orchestra Foundation, participated in the study (See Supplemental Material). Enrollment began in May 2013, the last patient completed the study in August 2017, and data analysis has been completed in February 2018.

Study design and objectives

The study was a national, prospective, multicenter, observational, post-market study of the effectiveness of commercially available devices [i.e., the MiniMed Paradigm REAL-Time insulin pump system (CSII with or without CGM); and the MiniMed Paradigm Veo insulin pump system with the Enlite™ sensor] (Medtronic, Poland). The primary objective was to assess the benefits of CSII and SAP on maternal glycemic control (HbA_{1c} and CGM data). Secondary objectives were: 1) to assess the prevalence of pregnancy complications (e.g., preterm delivery, low infant birth weight, neonatal care admissions) throughout pregnancy, during delivery, and during lactation for up to 6 weeks after delivery; 2) to evaluate the potential benefits of CSII and SAP on neonatal outcomes; and 3) to evaluate changes in patient-reported outcomes, such as concerns about hypoglycemia and satisfaction with diabetes treatment.

Study population

The study population consisted of women aged 18–45 years with T1DM who either intended to become pregnant within 12 months or were already in the early stages of pregnancy (≤ 16 weeks). Women were eligible for inclusion in the study if they had been treated with MDI for, at least, 3 months and had indications for

CSII, SAP or SIP. Women with type 2 diabetes, gestational diabetes or maturity-onset diabetes of the young (MODY) were excluded, as were patients using insulin pumps that had not been donated by the Orchestra Foundation. Women who required assisted fertilization technologies, or participated in any interventional clinical trial within 3 months prior to screening, were also excluded. Written informed consent was obtained from all patients before enrollment in the study.

Based on local data and experience, it was anticipated that in about two thirds of cases CSII would start during the first trimester of pregnancy (≤ 16 weeks). The estimated total sample size was 500 women, which included 100 with complete follow-up (from pre-conception until 6 weeks post-delivery), 300 enrolled up to the 16th week of pregnancy, and 100 who may be expected to be withdrawn for various reasons. Enrollment would stop when data from 100 participants with complete follow-up from pre-conception until 6 weeks post-delivery had been collected. A flow chart summarizing enrollment and termination procedures is shown in Figure 1.

Pre-conception care

There were 24 specialized centers in Poland with professional health care teams consisting of: a diabetologist, diabetes educator, nurse, and dietitian. All women with T1DM participating in the pregnancy planning program received intensive diabetes management in these clinics. The intensive diabetes management involved education on diet and carbohydrate counting, physical activity, folic acid supplementation, glycemic goals, self-monitoring of blood glucose (SMBG), and self-adjusting insulin dose. Care included frequent

outpatient visits, and hospitalization if necessary. All women were trained by a dietician and/or diabetes educator. The recommended standard caloric intake was 35 kcal/kg of body weight, of which 40–50% was to be covered by carbohydrates, 20–30% by fats, and 30% by proteins. Excessive weight gain was addressed by reducing daily food intake accompanied by a regular daily self-assessment of urine ketones. According to the Polish Diabetes Association recommendations in year 2015 [15], the therapeutic targets for all women planning a pregnancy or who are pregnant are: a) $HbA_{1c} < 6.1\%$, b) fasting SMBG within 60–90 mg/dl, and c) subsequent pre- and 1-hour postprandial SMBG within 60–120 mg/dl. The Association also recommends that all women planning a pregnancy receive a supplementation of folic acid. The glycaemia monitoring plan was highly structured, in terms of both timing and frequency, and was provided to all women by the diabetes educator. Women were requested to wear a CGM system or to perform SMBG 8 to 10 times a day using a blood glucose meter transmitting to an insulin pump: fasting, before, and one hour after main meals, at bedtime, and between 2–4 am.

Study procedures

Study visits and procedures are summarized in Table 1. All women had an initial pre-conception visit, with a second visit 12 ± 4 weeks after amenorrhea. Women who did not conceive within 12 months of the initial visit had a third visit at $12 \text{ months} \pm 2$ weeks. Women who were already pregnant at enrollment had the initial visit at the time of enrollment. All pregnant women were assessed after 24 and 36 weeks (± 2 weeks) of amenorrhea, at delivery, and 6 weeks after delivery (both ± 2 weeks). At each assessment, clinical data were recorded in electronic case report forms (eCRFs), and data from devices (pumps and glucose meters) were uploaded into CareLink™ Clinical software. Women who experienced a miscarriage kept their pump for an additional 3 months after the miscarriage, if they wished to continue insulin pump therapy.

A CareLink USB was provided for uploading blood glucose meter or insulin pump data to CareLink Clinical software. In addition, a blood glucose meter compatible with the CareLink Clinical software; insulin pump therapy consumables; and all necessary devices for insertion were provided. Except for the Enlite sensors, which are single-use devices, all devices were loaned to the study participants for the entire study period, after which they would be returned to the center investigators.

Approximately two thirds of the participants had been provided the Paradigm REAL-Time pump, and

the remaining were provided the Paradigm Veo pump. The participants using the Paradigm REAL-Time system could use CGM (i.e., the MiniLink™ transmitter and Sof-Sensor sensor) at their own expense, if the HCP agreed to this. The participants using the Paradigm Veo received as many Enlite sensors free of charge as their health care professional (HCP) considered necessary. All participants received adequate training using a standardized training checklist on the use of insulin pumps, CGM, and consumables. This training was provided by the HCP at the investigation center, or a Certified Product Trainer, based on local practice. All participants were to have shown good compliance with, and an ability to understand and use, their therapy, as assessed by the treating physician.

Data recorded

Clinical outcomes

Maternal HbA_{1c} levels before the initiation of insulin pump therapy were obtained retrospectively from medical records. HbA_{1c} was measured on 2–3 occasions during pregnancy, with a final measurement being made at the end of the study. Other clinical data collected included weight, BMI, daily insulin use, the number of SMBG measurements conducted per day (or self-reported by the participant), and the incidence of serious adverse events (e.g., severe hypoglycemia, diabetic ketoacidosis, miscarriage, hospitalizations). Concerns about hypoglycemia were assessed using the Hypoglycemia Fear Survey (HFS) at enrollment, on 2–3 occasions during pregnancy, and 6 weeks after delivery. Satisfaction with diabetes treatment was assessed by means of the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at the aforementioned occasions, and the DTSQc at pregnancy week 24 [39, 40]. Data on sensor and pump use during delivery, satisfaction with treatment during delivery, and additional participant-reported outcomes were also recorded.

The following neonatal outcomes were recorded: incidence rates of mode of delivery (e.g., i.e., normal, elective, cesarean section (CS), and emergency CS), gestational age at delivery, infant birth weight percentile [Large for Gestational Age (LGA), small for gestational age (SGA)], neonatal care admission, neonatal morbidity, pregnancy-related serious adverse events, and feeding status on discharge from hospital.

Adverse events

Serious adverse events were defined as: a) events leading to death; b) events leading to life-threatening illness or injury, permanent anatomical or functional impairment, or in-patient or prolonged hospitalization

Table 1. Study visits and procedures

	Visit 1 (Pre-conception)	Visit 2a* 12 weeks (± 4 weeks) amenorrhea	Visit 2b** 12 months (± 2 weeks) amenorrhea	Visit 1 (Pregnancy)	Visit 3 24 weeks (± 2 weeks) amenorrhea	Visit 4 36 weeks (± 2 weeks) amenorrhea	Visit 5*** Delivery (+ 2 weeks)	Visit 6 6 weeks (± 2 weeks) Post-delivery
Informed consent obtained	X			X				
Inclusion/exclusion criteria reviewed	X			X				
Patient identification number assigned	X			X				
HFS	X		X	X	X	X		X
DTSQs	X		X	X	X	X		X
DTSQc					X			
Demographic and clinical characteristics recorded on eCRF	X			X				
Carelink™ Clinical account created	X			X				
Insulin pump data uploaded to Carelink™ Clinical		X	X		X	X	X	X
Data from compatible blood glucose meter uploaded to Carelink™ Clinical		X	X		X	X	X	X
Patient training for devices checked	X			X				
Distributed devices recorded in eCRF and device tracking log	X			X				
Supplies distributed	X	X		X	X	X	X	
Follow-up eCRF completed		X			X		X	
Serious adverse events recorded		X	X		X	X	X	X
End of study eCRF completed			If no pregnancy					X
Devices returned			If no pregnancy					X

*If the patient is already pregnant at enrollment, procedures started from Visit 1 (Pregnancy); **not applicable for women becoming pregnant within 6 months; ***eCRF data collected within 2 weeks after delivery
eCRF — electronic case report form; HFS — hypoglycemia fear survey; DTSQ — Diabetes Treatment Satisfaction Questionnaire (s — status, c — change)

or medical or surgical intervention (particularly hypoglycemia or hyperglycemia); and c) events leading to fetal distress, fetal death or congenital abnormalities or birth defects. Potential device-related adverse events included: skin reactions to infusion set or sensor adhesive, inflammation or bruising at the insulin infusion site, or incorrect insulin delivery.

Statistical methods and analysis

All enrolled subjects who have participated in Orchestra Pregnancy Observational Study in Poland were included in the efficacy and safety analysis. Baseline information and demographic characteristics such as age, gender, weight, BMI, diabetes duration, insulin regimen, etc. were summarized. Medical information such as previous severe hypoglycemia and DKA history up to 12 months prior to study start was also summarized.

Clinical and safety data were summarized using descriptive statistics for all available groups: 1) all enrolled; 2) those who failed to achieve a pregnancy; 3) those who become pregnant after the pre-conception phase; 4) those already pregnant at enrollment.

The primary analysis investigated the change in HbA_{1c} from the beginning to the end of pregnancy. Secondary analyses included the following: the proportion of subjects achieving $HbA_{1c} < 6\%$, 6.5% , 7% , 7.5% , and 8% ; descriptive statistics for sensor glucose (e.g., mean, variability, percent in range and AUC) analyzed as overall and stratified by pregnancy outcome (no conception, delivery, miscarriage, etc.); and completeness of treatment phase (i.e., complete follow-up, pregnancy and 6 weeks after delivery, pre-conception phase only, etc.).

Other maternal outcomes, such as weight, BMI, daily insulin requirements (units) at the moment of the visit, and microalbumin excretion with albumin/creatinine ratio were also collected.

Initial results after completed recruitment are shown in Figure 2.

Discussion

Insulin pump therapy has been shown to improve quality of life in pregnant women with diabetes [31, 41]. The Orchestra Foundation facilitated use of insulin pumps by all pregnant women with type 1 diabetes in Poland; hence, all participants fulfilling study inclusion criteria were registered, and only those with contraindications to insulin pump therapy were excluded from the study. The clinical study intended to recruit as many women as possible during the pre-conception period: approximately 20–30% participation was anticipated.

The advantage of this study design was the use of insulin delivery devices with the same platform by all participants. All studied women were Caucasian

with T1DM. All study centers used the same devices and the same methods of education and training for participants. However, a limitation was that, although studies comparing the use of CSII and MDI have yielded inconsistent results [23, 29, 42–46], it was not possible to compare the results of pump use with a control group not using pump therapy and/or pump therapy supported by CGM. Nevertheless, this study offered a unique opportunity to follow a large patient population using standardized insulin-delivery devices to assess the prevalence of pregnancy complications and outcomes. It was also possible to compare the results of introducing pump therapy, with or without CGM, before and during pregnancy.

Author disclosure statement

JS¹ reports receiving lecturing and consulting fees from MSD, Bioton, Novartis, Medtronic, and Mylan; and has conducted clinical trials as co-investigator for Medtronic.

KC² has provided advisory services to Medtronic and Roche; attended conferences organized by Eli-Lilly & Company, Novo Nordisk, Roche, and Medtronic, as lecturer or contributor; reports receiving lecturing and consulting fees from Medtronic, Roche, and Novo Nordisk; and has conducted clinical trials as co-investigator for GlaxoSmithKline.

KC³ has conducted clinical trials as co-investigator for Medtronic, Eli-Lilly & Company, Novo Nordisk A/S, AstraZeneca AB, Boehringer Ingelheim, and Pfizer; provided advisory services to Medtronic, Eli-Lilly & Company, Novo Nordisk A/S; attended conferences organized by Eli-Lilly & Company, Novo Nordisk, and Medtronic as contributor; and reports receiving lecturing and consulting fees from Medtronic, Bayer AG, Eli Lilly & Company, Novo Nordisk A/S, Sanofi-Aventis, Boehringer Ingelheim, and Johnson&Johnson Sp. z o.o.

EW-O⁴ has conducted clinical trials as co-investigator for Medtronic and Novo Nordisk; provided advisory services to Medtronic, Eli-Lilly & Company, and Novo Nordisk; attended conferences organized by Novo Nordisk, Eli-Lilly & Company, and Medtronic as contributor; and received investigator fees in relation to lectures and study protocols.

KS, SR, and JS⁷ are employees of Medtronic.

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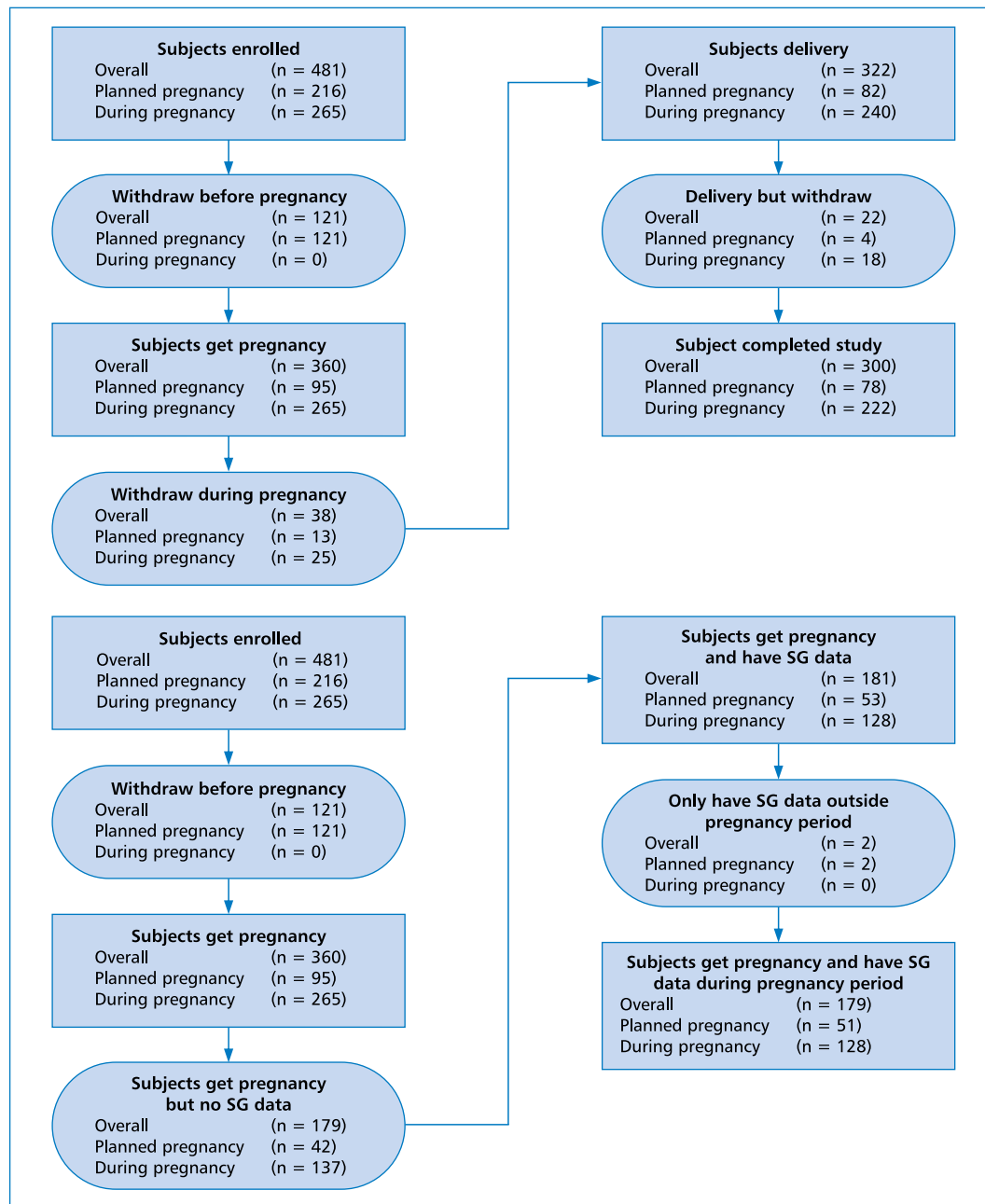


Figure 2. Initial data after completed recruitment

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